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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,997	09/18/2003	Carol Carter	FUNC-0017-CO1	6642

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,997	CARTER ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-91 and 93-134* is/are pending in the application.

4a) Of the above claim(s) *59-91 and 95-131* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93,94 and 132-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 29 May 2007. Claims 132-134 have been added. Claims 1-91 and 93-134 are pending. Claims 59-91 and 95-131 are withdrawn. Claims 93, 94 and 132-134 are under final rejection.

Claim Objections

The objection to claims 93 and 94 is **withdrawn** in response to Applicant's amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 93 and 94 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is **withdrawn** in view of the amendment newly limiting the compound to a peptide comprising a PTAP motif.

The rejection of claims 93 and 94 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement is **maintained and extended** to claims 132-134.

The instant claims are drawn to a method of inhibiting binding between TSG101 and HIV Gag protein, inhibiting HIV particle generation and thereby treating AIDS in a

mammalian patient comprising administering to said patient a peptide comprising a PTAP motif.

Examiner's rejection in the Action mailed on 05 June 2006 is as follows:

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Nature of the invention: The claims are drawn to a method of inhibiting HIV budding, treating HIV infection or preventing AIDS comprising administering a compound that binds TSG101 protein.

Breadth of the claims: The claims read on a genus of unspecified compounds that bind Tsgl01 proteins, which encompass siRNA, aptamers, ribozymes, antibodies, small molecule inhibitors, and Gag homologs. The claims are of excessive breath and encompass any give putative antiviral compound without providing any meaningful structural limitations concerning that compound. The disclosure simply fails to support such breadth in the claim language.

Working examples: The disclosure fails to provide any working embodiments that meet the claimed limitations. While there is one cell culture example is disclosed for the species of Gag p6 late domain, this compound does not represent all other TSG101-inhibitors that fall within the scope of the invention. There are no other examples of TSG101-binding compounds. No in vivo working example of any TSG101-binding compound is disclosed in the specification.

Guidance in the specification: The specification provides no guidance regarding practice of the claimed method. The amount of direction is limited to a cell culture assay to determine the binding between HIV Gag p6 late domain and Tsgl01 (Example 1) and the amount of mature HIV particles (Example 2). There is no evidence that shows any correlation with in vivo efficacy. First of all, there is no structural guidance to the broad genus of unspecified TSG101-binding inhibitors. In other words, the specification fails to disclose which chemical structures are critical for binding to TSG101 and which structures are required for anti- HIV budding. Thus, the specification is no more than an undue invitation by the applicant to further experimentation to identify putative HIV budding inhibitors and determine their structures. Second, there is no teaching about the therapeutic properties such as the binding specificity, selectivity and affinity, oral bioavailability, cellular uptake, toxicity, lethal dose, and side effects. Lastly, there is not even a test to determine the efficacy and resistance of the claimed

genus of Tsgl01 inhibitors to confirm the cell culture inhibitory results. *In vitro* testing is, at most, a useful tool for screening potential anti-viral agents but is not predictive of *in vivo* effectiveness. *Ex Parte Balzarini* (BdPat App&Int) 21 USPQ2d 1892. One skilled in the art would not associate successful *in vitro* testing results with successful *in vivo* AIDS treatment without any knowledge of the pharmacokinetic profile, therapeutic and/or prophylactic effect in a patient. Therefore, the disclosure does not correlate with treating HIV infection or preventing AIDS, especially when the subject may be a person.

State of the prior art: At the time the invention was made, a TSGI01 binding compound for the treatment of HIV is not considered routine in the art. It has been well known in the prior art (Hendrix, 2000, first and last ¶; Gait, 1995) that the development of suitable HIV- 1 therapeutics has been an arduous and empirical process, often ending in failure. This is due to a number of factors: (1) failure to understand the molecular determinants modulating many viral protein and host cell factor interactions; (2) failure of *in vitro* tissue culture studies and *in vivo* animal models to adequately predict clinical efficacy; (3) failure of many compounds to have acceptable pharmacological profiles despite initial favorable *in vitro* and *in vivo* activities; and (4) failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The challenges of developing efficacious anti-HIV agents are best summarized by Gait and Karn (1995) who state in the Conclusions (p.37): There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivity for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage.

Predictability of the art: The art of HIV treatment is highly unpredictable because the effect of antiretroviral treatment appears to change due to pharmacokinetic variation, fluctuating adherence, the emergence of drug resistant mutations and/or other factors. Inadequate drug concentrations can result from a number of factors including non-adherence, pharmacokinetics, and lack of drug potency. In addition, anatomical sanctuary sites may exist where drug concentrations do not achieve adequate levels despite apparent therapeutic serum drug concentrations. HIV replication can occur in such settings, and the selective pressure of antiretroviral therapy leads to the emergence of HIV harboring drug-resistant mutations. Thus, a key element in future drug design strategies is to understand how drug resistance mutations affect the interaction of the drug with its target, and to then develop compounds with the adaptability to inhibit these variants along with wild-type HIV (Yin, 2006). Therefore, efforts to develop effective treatments must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations.

Amount of experimentation necessary. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In the instant case, a TSG101 inhibitor as a HIV drug is not considered routine in the art. The disclosure fails to address any of the aforementioned caveats in the development of an antiviral agent. Without sufficient guidance to the safety, tolerability, and antiviral effect, the experimentation left to those skilled in the art is undue or unreasonable under the circumstances.

For the reasons discussed above, it would require undue and unpredictable experimentation for one skilled in the art to use the claimed method.

Applicants argue that claims are not confined solely to the operative examples set forth in the specification and that the Examiner did not discuss specific Wands factor or factors sufficiently. However, Applicants failed to respond to each of Examiner's detailed Wands factor analysis as reiterated above. It is evident that Examiner is not relying solely on the lack of operative examples in the specification to determine whether the instant claims are enabled by the description in the application. It is not disclosed whether the anti-HIV peptide acts on a target that is conserved among all hosts. The Gag protein is neither conserved between the two HIV serotypes, HIV-1 and HIV-2, nor among the abundant strains or quasi-species of HIV. Therefore, the peptide binding affinity/avidity is questionable. Applicants have not provided any evidence that correlates cell culture inhibition assay data with *in vivo* drug potency, especially given that the prior art teaches against the correlation between *in vitro* success and *in vivo* efficacy because the prior art unequivocally cautions against the problems of short half-life, viral drug-resistance, poor oral bioavailability, serum protein sequestration, low plasma concentration in developing new anti-HIV agents. None of the listed problems were adequately addressed in the cell culture example in the instant application.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly required undue experimentation from the skilled artisan to use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of claims 93 and 94 under 35 U.S.C. §102(e) as being anticipated by Zavitz *et al.* (US 2004/0109861, effectively filed 14 March 2001) is **withdrawn** in response to the claim amendment newly limiting the claimed invention to treatment in a mammalian patient.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
01 August 2007

Louise Humphrey, Ph.D.
Assistant Examiner